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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/547,066 | 05/22/2006 | Marianne Bruggemann | M0106.70004US00 | 4387 |

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WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

| EXAMINER | |
|---|---|
| LI, QIAN JANICE | |
| ART UNIT | PAPER NUMBER |
| 1633 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/547,066 | BRUGGEMANN, MARIANNE | |
| | Examiner | Art Unit | |
| | Q. JANICE LI | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-15 and 17-73* is/are pending in the application.

4a) Of the above claim(s) *9, 10, 13, 15,17, 19, 22-28,30-38, 41-59,62-69,72,73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11,12,14,15,18,20,21,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 August 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/16/2010 has been entered.

The amendment, declaration of Dr. Bruggemann and remarks filed 2/16/10 are acknowledged. Claim 16 has been canceled. Claims 1-8, 11, 12, 14, 15, 18, 20, 39, 40 have been amended and claims -8, 11, 12, 14, 15, 18, 20, 21, 39, 40 are under current examination.

It is noted in the 2/16/10 amendment, claim 21 has erroneously been labeled as "withdrawn" and claim 22 has been labeled "currently amended". However, Claim 21 should be under current examination and claim 22 is withdrawn from consideration as indicated in the previous Office action. The Office believes that this is an inadvertent error, and hence treated claims as if claim 21 has been amended to drawn to a genetically modified mouse. Appropriate correction is required in the response to this Office action.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims and persuasive argument will not be

reiterated. Upon further consideration, a new ground of rejection is necessitated. The arguments in 2/16/10 response would be addressed to the extent that they apply to current rejection.

### *Election/Restrictions*

Applicant's election of Group I and species election, drawn to a non-human mammal having all endogenous IgH VDJ segments, are acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-8, 11, 12, 14-16, 18, 20, 21, 39, 40 read on the elected invention.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8, 11, 12, 14, 15, 18, 20, 21, 39, 40 are rejected under 35 U.S.C. 103(a) as being obvious over *WO 98/54348* (IDS) in view of *Rajewsky et al.* (USP 6,570,061, IDS), and *Li et al.* (PNAS 1996;93:6158-62).

*WO 98/54348* teaches transgenic mice whose genome does not comprise a nucleic acid sequence encoding any endogenous immunoglobulin heavy chain constant region locus (IgH C) polypeptide (see e.g. the abstract and example I, particularly page 9). In the targeting construct, a mouse IgH 3' enhancer sequence is present and operably linked to a selectable marker gene (e.g. page 7). The mice disclosed by *WO*

*98/54348* differs from instantly claimed in that the deletion technique used requires deletion of the entire IgH locus and it appears that nucleic acid sequences encoding the endogenous IgH V, D, J segment might be absent.

*Rajewsky* supplemented *WO 98/54348* by establishing it was well known in the art to selectively deleting a segment of the IgH locus. *Rajewsky* discloses transgenic mice whose genome comprising targeted gene knockout of the mouse IgH C genes and replacing such with the human IgH constant region gene (e.g. see the abstract and claims 1-3). Hence the genome of these genetically modified mice does not contain a nucleic acid encoding an endogenous IgH constant region locus polypeptide, but contains all the IgH variable region, D and J segments. *Rajewsky* further teaches the mice were obtained either through conventional gene targeting or by use of the Cre-loxP recombinant system. In working examples, a targeting vector containing an IgL C gene enhancer sequence (MC$\kappa$) and a selectable marker neomycin gene was used (e.g. column 8, lines 45-64). *Rajewsky* also teaches breeding the transgenic mice to produce progenies (e.g. col 7, lines 34-44). *Rajewsky* differs from instant claims in that the patent did not explicitly teach targeting the entire IgH constant region. In working examples, only a portion of the C region was deleted and replaced (C$\gamma$1), such as indicated in claims 7 and 8, wherein the mouse contains some of the endogenous IgH-C. However, given the levels of the skilled as established by *Rajewsky*, one would know how to make a mouse having total depletion of the endogenous IgH-C gene if intended, e.g. by targeting each of the multiple regions individually or targeting a large fraction of the constant region as taught by *Li*.

*Li* supplemented *WO 98/54348* in view of *Rajewsky* by establishing the technique of selectively deleting a large gene fragment was known in the art. *Li* teaches generating mice with a 200-kb deletion of the amyloid precursor protein gene using Cre recombinase-mediated site-specific recombination, wherein two loxP sites were inserted upstream and downstream flanking the genome region to be deleted, followed by exposure to a cre recombinase.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the mouse as taught by WO 98/54348 by selectively knockout a part or the entire constant region of IgH chain using the targeting strategies as taught by *Rajewsk* or *Li* with a reasonable expectation of success. Given the knowledge of the skilled in the art, the limitation falls within the bound of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

***Response to Arguments***

In the declaration and remarks, the applicant argues that *Rajewsky* use a targeting construct harboring a human constant region gene and target mouse Cγ or Cκ in a mouse ES cell in a single homologous recombination event, while instant application employed methods to achieve deletion of the entire IgH C locus (all eight IgH C genes) using two different targeting constructs. Applicant also argues that genomic loci harboring highly repetitive sequences such as the IgH C locus, are known

to be difficult to target as the repetitive sequences are likely to interfere in homologous recombination events.

The argument has been fully considered but not found persuasive in view of the newly cited *Li* reference, wherein a 200kb genomic sequence (about the size of instant IgH C loci, see fig. 1 of the Specification), known to be difficult to target, was deleted using two loxP-site insertions into the 5' and 3' proximal regions of the APP gene followed by introducing a Cre recombianse expression vector, which selectively deleted the entire gene by homologous recombination in ES cells. Hence, the means for deleting a large gene fragment in a mouse ES cell and making a mouse from the ES cell was known in the art and reasonably predictable.

The applicant goes on to argue that until the production of the IgH C locus knock-out of the present invention, it was uncertain that an animal or cell lacking endogenous IgH C to such extent that no functional endogenous heavy chain polypeptide is expressed could be generated. The applicant also asserts it was expected that if such an animal could be generated, they would not be viable since it would be severely immunocompromised.

The argument has been fully considered. Although the recited reasoning in the declaration provides some persuasive secondary consideration for generating mice *lacking* entire endogenous IgH C region *and lacking* any functional IgH C polypeptide, in the past publications such have been compensated by introducing a corresponding exogenous region, such as a human IgH C region as taught by *Rajewsky* or *WO 98/54348*. Since pending claims as written do not exclude the presence of a

corresponding exogenous IgH C region locus, the scope of the claims are not commensurate with the scope of the secondary consideration.

Applicants are reminded the unexpected results should be commensurate with the scope of the disclosure. The court has determined, "WHETHER THE UNEXPECTED RESULTS ARE THE RESULT OF UNEXPECTEDLY IMPROVED RESULTS OR A PROPERTY NOT TAUGHT BY THE PRIOR ART, THE "OBJECTIVE EVIDENCE OF NONOBVIOUSNESS MUST BE COMMENSURATE IN SCOPE WITH THE CLAIMS WHICH THE EVIDENCE IS OFFERED TO SUPPORT." IN OTHER WORDS, THE SHOWING OF UNEXPECTED RESULTS MUST BE REVIEWED TO SEE IF THE RESULTS OCCUR OVER THE ENTIRE CLAIMED RANGE. *IN RE CLEMENS*, 622 F.2D 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)" ((MPEP 716.02(d), emphasis added)). In the instant case, the secondary consideration only supports mice lacking both endogenous and exogenous IgH C loci.

Further, the secondary consideration does not apply to the scope of the claims drawn to a mouse cell that dose not comprise a nucleic acid sequence which itself encodes any IgH C polypeptide, since whether such mouse could be generated or its viability would not be a concern for making a cell as taught by the combined teachings. Accordingly, claim 3 is also rejected because of the scope of the claim.

Accordingly, the rejection is appropriate considering the full scope of the pending claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI** whose telephone number is **571-272-**

**0730**. The examiner can normally be reached on 9 AM -7:00pm, Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

*/Q. JANICE LI, M.D./*
*Primary Examiner, Art Unit 1633*